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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/773,394
Filing Date: January 31, 2001
Appellant(s): WIKLUND ET AL.

Edward A. Meilman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 28, 2006 appealing from the Office action mailed July 6, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

US Patent 5,310,768	Vinnars	May 10, 1994
US Patent 5,719,119	Veech	February 17, 1998
US Patent 5,219,330	Bollish et al.	June 15, 1993

Tanconic "Sprague Dawley Outbred Rats," http://www.taconic.com/anmodels/sprague.htm

(9) Grounds of Rejection

Claim Rejections 35 U.S.C. 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-2, 4-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 recites "pharmaceutical agents consisting essentially of (a) a first composition containing at least one of alpha-ketoglutarate and alpha—ketoglutaric acid and being devoid of ammonium, and (b) a second composition containing ammonium and be devoid of a alpha-ketoglutarate and alpha-ketoglutaric acid." As currently amended, the claim further requires "wherein any composition administered containing at least one of alpha-ketoglutarate and alpha-ketoglutaric acid is devoid of ammonium." Claim 15 recites "pharmaceutical dosage

unit comprising a first pharmaceutical composition comprising at least one of alpha-ketoglutarate and alpha—ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium, and a second pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and be devoid of a alpha-ketoglutarate and alpha-ketoglutaric acid" Interpretated broadly, the claims read on separate compositions containing alpha-ketoglutarate and ammonium respectively. However, the application, as originally filed, lacks support for such separate composition. Particularly, the application provides no support for "composition containing at least one of alpha-ketoglutarate and alpha—ketoglutaric acid and ***being devoid*** of ammonium," "composition containing ammonium and ***being devoid*** of a alpha-ketoglutarate and alpha-ketoglutaric acid," "wherein any composition administered containing at least one of alpha-ketoglutarate and a-ketoglutaric acid is devoid of ammonium." in claim 1, and "pharmaceutical composition comprising at least one of alpha-ketoglutarate and alpha—ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium," " pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and being devoid of a alpha-ketoglutarate and alpha-ketoglutaric acid" in claim 15.

3. Further, claim 1 as currently amended, require "concomitant and ***separate***" administration. The application as originally filed lacks support for "***separate***" administration.

4. Furthermore, claim 15 recites "*pharmaceutical dosage unit comprising a first and second separate pharmaceutical compositions,* the first composition comprising at least one of alpha-ketoglutarate and alpha—ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium, and a second pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and be devoid of a alpha-ketoglutarate and alpha-

ketoglutaric acid" The application as originally filed provides no support for such pharmaceutical dosage unit.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-2, 4-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 1 recites "***concomitant and separate*** administration." The phrase is confusing in that how the administration is carried out concomitantly and separately. The specification or the claims provide no further clarification as the meaning of "concomitant and separate administration." The claim is indefinite as to how the administration is carried out.

Claim Rejections 35 U.S.C. 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Veech (USPN 5,719,119) and Vinnars (USPN 5,310,768), in further view of Taconic (http://www.taconic.com/anmodels/spragued.htm), and Bollish et al. (US 5,219,330).

The claims as currently amended, are directed to a dosage unit (a composition) comprising a first and second separate pharmaceutical composition, the first composition comprising at least one of alpha-ketoglutarate and alpha-ketoglutaric acid and being devoid of ammonium, and the second pharmaceutical composition comprising ammonium, and being devoid of alpha-ketoglutarate and alpha-ketoglutaric acid; and method of concomitant and separate administration of this two composition. The administration herein claimed is construed as administering the two composition wherein the two compositions are separate before the administration, in view of the limitation "wherein any composition administered containing at least one of alpha-ketoglutarate and a-ketoglutaric acid is devoid of ammonium."

Veech (USPN 5,719,1 19) teaches a parenteral nutrition solution comprising carboxylic metabolite anions, such as lactate and/or alpha-Ketoglutarate, (0.1-150 mMole/L) and cation such as ammonium and sodium (0.1-150 mMole/L), See, particularly, columns 5. Particular examples comprising alpha-ketoglutarate and ammonium is disclosed. see Table 9, co1.20, examples 1.4-1.5. Veech also teaches the employment of the parenteral nutrition solution comprising alpha-ketoglutarate in a method of normalizing muscle and organ function, see claims 5 and 6 for example. Veech further teaches that post-traumatic or post-operative patients suffer from a negative nitrogen balance, col.7, line 55 to column 8 line 7. Veech also teaches alpha ketoglutarate and ammonium in an amino acid solution containing glutamate which can control the redox state of the mitochondria and therefore be useful in nitrogen- containing pharmaceutical compositions, see col. 13 line 5 to col. 14 line 20. The parenteral composition is for intravenous administration. See, column 21, lines 1-8. Infusion rate of the composition to a

Sprague Dawley male rate is about 2 ml/hour. It is noted Sprague Dawley male rat is normally less than 500 g in weight. See Prague Dawley Outbred rats (Taconic reference).

Vinnars (USPN 5,310,768) teaches a method of treatment of post operative and Post-traumatic patients for improving glutamine content in skeletal muscle and preventing the reduction of protein synthesis capacity, hence also, improve the nitrogen balance and even make it positive by administering alpha-ketoglutarate, alone or in combination with other actives, see col. 2, lines 54-63 and abstract in particular. Vinnars teaches that the amount of alpha-ketoglutarate is at least 0.1g/kg body weight/day (which amounts to 312.5 micromoles/kg body weight per day), see col. 3, lines 6-12.

Veech and Vinnars do not particularly teach the dosing regimen herein in terms of micromoles per kilogram per minute, nor do they teach the administration of two separate compositions. Neither does it particularly teach the employment of a particular salt of ammonium.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to a dosage unit, wherein alpha-ketoglutarate and/or alpha-ketoglutaric acid, and ammonium are present separately in two composition, but are ready for the concomitant administration for preserving bodily protein, because both alpha-ketoglutarate and ammonium are known to be useful in methods of treating post-operative/post-traumatic patients and normalizing/preserving skeletal muscle glutamine/nitrogen content. Concomitant administration of the two agents which are known to be useful to improve nitrogen balance and preserve skeletal muscle individually into a single composition useful for the very same purpose is prime facie obvious. See In re Kerkhoven 205 USPQ 1069. The employment of salts of known actives

is within the skill of the Skilled Artisan and is therefore obvious. Furthermore, water, employed by Veech as the carrier, are both acceptable in parenteral composition and oral composition.

As to the particular concentration or dosing regimen herein, note it is well understood that optimization of effective amounts or and administrative regimens in pharmaceutical art is considered within the skill of the artisan. *Ex parte Skuballa* 12 USPQ2d 1570. Particularly, it is noted that the particular regimens herein are well within the range disclosed by the prior art. For example, assume a composition comprising 100 mMole/L each of alpha-ketoglutarate and ammonium, is administered with a infusion rate of 30 mL/hour (or 0.5 mL/min) to a Patient with 50 kg, the rate would be 1 $\mu mol.kg^{-1}.min^{-1}$, well within the claimed range. It is well understood that "wherein the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F. 2d 454, 456, 105 USPQ 233,235 (CCPA 1955). Further, the optimization of a result effective parameter, e.g., effective amounts, is considered within the skill of the artisan. See, *In re Boesch and Slaney* (CCPA) 204 USPQ 215. Note normal operatable Intravenous infusion rate is in the range of 1 mL/hour to about 300 mL/hour in a duration of 1-24 hours. See, e.g., column 2, lines 55-68, column 5, lines 34-52 in Bollish et al. As to the limitation that requiring alpha-keto-glutarate and ammonium in separate compositions but with a dosage unit, the examiner contend that such dosage unit (and its concomitant administration) would have been obvious to a mixture of alph-glutarate and ammonium since such rearrangements provide no difference as to the therapeutical utility. One of ordinary skill in the art would have view such rearrangement as a obvious alternative of the mixture.

(10) Response to Argument

As to the written description rejections, appellants contend that the alleged new matters are supported by the disclosure at page 12, particularly the examples. The arguments are unconvincing. First, the disclosure never mentioned that ammonium composition is devoid of alpha-keto-glutarate, nor glutarate composition is devoid of ammonium; second, the examples discloses experiments on piglets, the experiments begins with infusion of one compound last for 240 min, and start infusion of second compound 60 min after the start of the first compound. The disclosure never state the second infusion is carried out in a *separate second* infusion line; third, the application never advances the experimental model in page 12 as the therapeutical method herein claimed which encompass human, and with further detailed requirements. Therefore, the application as originally filed does not support the new limitation recited in the claims.

Regarding the rejections under 35 U.S.C. 112, second paragraph, it is noted the phrase is confusing in that how the administration is carried out concomitantly and separately. *The specification or the claims provide no further clarification* as the meaning of "concomitant and separate administration." The claim is indefinite as to how the administration is carried out.

As to the rejections under 35 U.S.C. 103, one of ordinary skill in the art would have view the concomitant administration of two agents as obvious alternative of administering the mixture of the two ingredients, absent evident to the contrary. Such rearrangement of the components without changing the utility is deemed to be obvious to one of ordinary skill in the art. See, In re Japikse, 181 F.2d 1019, 86 USPQ 70 (CCPA 1950); In re Kuhle, 526 F.2d 553, 188 USPQ 7 (CCPA 1975); In re Dulberg, 289 F.2d 522, 523, 129 USPQ 348, 349 (CCPA 1961). Further, even assume the claimed invention require the second infusion, such limitation would not make

the claimed invention patentably distinct from the prior art. Note, Vinnars teach an alpha-ketoglutarate composition void of ammonium. It would have been obvious to use Vinnars' composition with another composition comprising ammonium in view the fact that both alpha-ketoglutarate and ammonium are known to be useful for the same purpose. Further, the prior art teach the infusion of the mixture of the two ingredients. The infusion of the two ingredients separate but concomitant in two infusion is indeed different form the prior art, but not in a patentable distinct way. The application provides no evidence that the separate infusions are actually better than the single infusion in the aspect of therapeutic efficacy. Obviously, the separate infusion is a bit of inconvenience compared to the single infusion. However, this inconvenience would not make it patentable distinct. "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132.

As to the increase of infusion of ammonium, it is noted that the art permit a large range as to the infusion rate, therefore, the variation of infusion rate within the art recognized range is within the purview of the artisan, absent evidence to the contrary.

In response to appellant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., increase ammonium load while keep alpha-Ketoglutarate load constant) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The examiner notes that the claimed invention requires the concomitant of ammonium and alpha-ketoglutarate and do not require the ammonium or alpha-ketoglutarate be used alone. Therefore the arguments that the cited references do not teach to use ammonium alone are irrelevant to the rejections.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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